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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,478	12/14/2001	Robert A. Kay	1040-3	5212

7590 11/12/2003

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	13

DATE MAILED: 11/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/017,478	KAY ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Receipt of the Amendment filed 09/02/03 is acknowledged.

Claims 1-18 are pending. Claim 1 has been amended to correct a typographical error only. No other amendments were made. Claims 1-18 stand rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (US Pat. No. 6, 042,849).

Richardson teaches an oral pharmaceutical composition comprising a dual layer combination tablet which is divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine, whereby the intestine-release portion contains magnesium compounds/magnesium salts in combination with additional active agents and therapeutic substances, such as calcium and calcium salts (see reference column 6, line 62 through col. 11, line 55).

According to Richardson, upon oral ingestion of the tablet, agents of the immediate release layer dissolve rapidly in the stomach and are available for immediate absorption in the gastrointestinal tract. The polymer matrix of the controlled release layer, having been given an enteric coating in the granulation process with Eudragit, does not dissolve in the acid pH of the stomach, but remains intact until it passes to the upper part of the small intestine, where the enteric coating dissolves in the more alkaline environment of the intestine (col. 11, lines 25-33).

The magnesium is present either as magnesium salts, other magnesium compounds that release magnesium ions when ingested, or both. Magnesiums that can be used are, for example, magnesium citrate, magnesium acetate, magnesium ascorbate, magnesium oxide and the like (col. 6, line 62 through col. 7, line 39).

Richardson teaches that the compositions and dosage forms are useful for treating magnesium deficiencies, particularly in treating magnesium and metabolite deficiencies that are characteristic of specific segments of the population (col. 11, lines 44-47).

Additional active agents include calcium and calcium salts (about 400 mg to about 1200 mg) for the treatment of specific conditions, and can be optionally combined with vitamin D for treating conditions in which hypomagnesia adversely impacts calcium utilization (col. 7, line 62 through col. 8, line 1).

The pharmaceutical composition can be formulated into various suitable dosage forms, including tablets, (gelatin) capsules, a solution, a suspension and a powder (col. 4, lines 57-64); (claim 11).

Suitable enteric materials include fatty acid mixtures, methacrylic acid polymers and copolymers, ethyl cellulose, and cellulose acetate phthalates. Specific examples are methacrylic acid copolymers sold under the name Eudragit® (see col. 8, lines 42-65).

According to Richardson, acid-resistant films of these types are particularly useful in confining the release of the magnesium lactate and magnesium citrate to the post-gastric environment. Acid-resistant films can be applied as coatings over individual particles of the components of the formulation, with the coated particles then optionally compressed into tablets. An acid-resistant film can also be applied as a layer encasing an entire tablet or a portion of a tablet where each tablet is a single unit dosage form (col. 8, line 66 thru col. 9, line 17).

Example 2, at col. 10, line 35, demonstrates a dual layer tablet, comprising an immediate release layer that disintegrates in the stomach and a controlled release layer for release into the intestine.

Regarding the instantly claimed ratios and pH dissolution points, it appears that Richardson teaches similar amounts of calcium and magnesium which read on the applicants claimed ranges, but does not teach the instant pH dissolution amounts. It is deemed obvious to one of ordinary skill in that suitable amounts or percentages can be determined through routine or manipulative experimentation to arrive at the best possible outcome. In addition, there is no criticality seen in the instantly claimed ratios and percentages since Richardson explicitly teaches a magnesium/calcium dosage formulation comprising similar ingredients and components for the treatment of magnesium deficiencies as similarly desired by the applicant.

Claims 13, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson *et al.* (US Pat. No. 6, 042,849), as applied to claims 1-12 and 15-17, and further in view of Krishnamurthy *et al.* (US Pat. No. 5,811,126) or Tencza (US Pat. No. 4,339,428).

Richardson, as discussed above, teaches an oral pharmaceutical composition comprising a dual layer combination tablet which is divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine, whereby the intestine-release portion contains magnesium compounds/magnesium salts in combination with additional active agents and therapeutic substances, such as calcium and calcium salts (see reference column 6, line 62 through col. 11, line 55).

Richardson is deficient only in the sense that he does not teach the instant selection of calcium salts.

Krishnamurthy teaches a controlled release pharmaceutical composition for oral administration comprising a mixture of magnesium salt and calcium salt, whereby suitable calcium salts that may be used include, calcium phosphate, calcium chloride, calcium carbonate, calcium acetate and calcium gluconate, for example. The calcium can comprise from about 1 to about 6% by weight of the composition (see reference col. 3, line 34 through col. 4, line 28) and abstract.

Therefore it would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Krishnamurthy within Richardson because Krishnamurthy explicitly teaches a controlled release magnesium/calcium combination mixture wherein any particular calcium salt can be used along with an active agent for forming the composition into tablets or capsules and similarly Richardson teaches a controlled release pharmaceutical composition comprising magnesium with calcium and calcium salts for treating hypomagnesia. The expected result would be an improved and highly effective dosage formulation for the treatment of magnesium deficiency and related disorders.

The teachings of Richardson have been discussed above. Richardson is deficient only in the sense that he does not teach the instant selection of calcium salts.

Tencza teaches an oral pharmaceutical formulation comprising a combination mixture of magnesium carbonate and calcium carbonate together with a magnesium oxide component (see reference col. 1, lines 14-27); (col. 2, lines 38-58); (col. 4, lines 50-66); Example 1 and abstract. According to Tencza, good disintegration rates are obtained when the alkaline material consists of a combination of magnesium oxide and/or magnesium hydroxide, magnesium carbonate and calcium carbonate.

Therefore, it would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Tencza within Richardson because Tencza explicitly teaches an oral dosage formulation comprising a magnesium carbonate/magnesium oxide/calcium carbonate mixture whereby good disintegration rates are obtained through the use of the formulated ingredients mixture and similarly Richardson teaches a combination formulation comprising magnesium salts and compounds with calcium salts and compounds for the treatment of hypomagnesia. The expected result would be an improved oral formulation, having better disintegration rates, for the administration of magnesium and calcium components to treat magnesium deficiencies as similarly desired by the applicant.

Furthermore, regarding the instant combination of magnesium with calcium or phosphate, the examiner notes, that for the treatment or correction of mineral or vitamin deficiencies, nutrients must work synergistically. There is a cooperative action between certain vitamins and minerals, which work as catalysts, promoting the absorption and assimilation of other vitamins and minerals. Correction of a deficiency of one vitamin or

mineral requires the addition of others, not simply replacement of the one in which you are deficient. It is realized that with magnesium deficiency, supplements needed for assimilation would be: calcium, phosphorous, potassium, vitamins C and D and vitamin B_6, for example. Therefore, there are no unexpected results that accrue from the applicant's use of the claimed combination.

Response to Arguments

Applicant's arguments filed 09/02/03 have been fully considered but they are not persuasive.

Firstly, the applicant argued regarding the rejection of claims 1-12 and 15-17 over Richardson US '849 stating, "The dual layer combination tablet combines calcium and magnesium so that they are simultaneously released into the body. Richardson does not disclose the sequential release of first calcium and then magnesium. The use of a time release component to limit the interaction of calcium with magnesium is neither taught nor suggested by Richardson."

These arguments have been fully considered, but were not found to be persuasive. Richardson teaches a dual layer tablet wherein the components are divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine, and optionally in a sustained-release manner over a period of time (col. 9, lines 35-41).

Richardson teaches that a delayed, post-gastric, prolonged release of the active ingredients in the small intestine can be achieved by encasing active agents or by encasing hydrophilic, water-swellable polymers containing the active agents, in an enteric (acid-resistant) film. Richardson states that acid-resistant films (i.e., methacrylic acid polymers, cellulose acetate pthalates) are particularly useful in confining the release of the magnesium lactate and magnesium citrate to the post-gastric environment. The 'controlled' or 'sustained' or 'time-release' delivery are equated to describe the type of active agent delivery that occurs when the active agent is released from a delivery vehicle at an ascertainable and manipulatable rate over a period of time, rather than being dispersed immediately upon entry into the digestive tract or upon contact with gastric fluid.

Secondly, the applicant argued, "Richardson does not disclose that calcium is included in either the first or second layer of the dual layer tablet, nor does he teach a preference for calcium in either the immediate release layer or in the delayed release layer."

These arguments have been fully considered, but were not found to be persuasive. According to Richardson, upon oral ingestion of the tablet, agents of the immediate release layer dissolve rapidly in the stomach and are available for immediate absorption in the gastrointestinal tract. Calcium and calcium salts are taught as additional active agents. Richardson states that a slower, more sustained release of the active agents can be achieved by placing the active agents in one or more delivery vehicles that inherently retard the release rate. The applicants argument that a

preference for calcium in the immediate or delayed release layer is not taught, is therefore not persuasive since Richardson clearly teaches calcium and its salts in combination with magnesium compounds wherein the magnesium compounds are provided in sustained and controlled release forms and contain enteric coatings for release only in the intestine. Hence, calcium would be construed as being contained in the immediate release layer of the tablet. The art clearly teaches confining the release of magnesium compounds to the post-gastric environment.

Next, the applicant argued, "There is no teaching nor suggestion in Richardson that calcium can be in a layer of a dual layer tablet without being combined with magnesium. Richardson does not teach a formulation or a two-layer tablet containing calcium and magnesium where the two components are not simultaneously released into the body. Moreover, the '849 patent does not teach the benefits of separating the calcium component from the magnesium component as required by the present claims."

These arguments have been fully considered, but were not found to be persuasive. Richardson exemplifies the combination of magnesium compounds with Vitamin E and does not explicitly exemplify magnesium with a calcium component in the examples. However, Richardson clearly discloses the use of calcium and its salts as additional active agents in the formulation, whereby magnesium compounds are confined in terms of sustained or controlled release rates for delivery into the intestine. Richardson does not state that the calcium be contained in the same layer as the magnesium component, and therefore one would conclude that the calcium component can be contained in a separate and distinct layer than that of the magnesium

component. Furthermore, it is of no moment that the prior art explicitly teach the benefits of separating the calcium from the magnesium component, merely that the prior art teach and recognize the presence of similar ingredients, in this case, magnesium and calcium components, in a similar functional manner as intended by the applicants is sufficient. Richardson focuses on the teaching that the magnesium components are confined to releasing at delayed or sustained release rates to the post-gastric environment.

The applicant argued, "Richardson does not teach that the interaction of calcium with magnesium prevents the efficient absorption of magnesium, nor does Richardson teach formulations containing calcium and magnesium should include a means for limiting their interaction."

These arguments were thoroughly considered, but were not persuasive. Richardson teaches a dual layer tablet, one portion, which fully releases its components in the stomach upon ingestion and the other protected by an acid-resistant coating for release only in the intestine. The tablet contains magnesium and calcium components. One of ordinary skill in this art would be well aware of suitable combinations of interactive agents to achieve effective results without contributing to adverse or detrimental effects.

Next, the applicant argued, "The Office Action states that Richardson discloses a formulation with a delayed release of both magnesium and calcium in the intestine. Unlike Richardson, the present composition does not delay release of both magnesium and calcium in the intestine."

These arguments have been considered, but were not found to be persuasive. The examiners' recitation of magnesium compounds/salts in combination with additional active agents was not to be construed as both the magnesium and calcium components being delayed release, as interpreted by the applicant. Rather, it was pointed out that Richardson along with magnesium components, also teaches calcium and its salts, wherein the tablet is divided into two portions, one that is fully released into the stomach upon ingestion and the other protected by an acid-resistant coating for release only in the intestine. Nowhere in the Richardson patent does it teach that the calcium component is contained in a delayed release form. The objective of Richardson is to provide advantages in terms of controlling and sustaining the release of magnesium in locations along the digestive tract wherein magnesium will have its greatest effectiveness as a therapeutic agent, thus improving the control over the clinical bioavailability of magnesium.

The applicant argued over the rejection of claims 13, 14 and 18 over the '849 patent in view of Krishnamurthy (US '126) or Tencza (US '428) stating, "Krishnamurthy teaches mixing calcium and magnesium together and does not teach nor suggest preventing them from interacting when released in the body. Krishnamurthy when combined with Richardson, does not make the present invention obvious since neither reference discloses a composition which releases calcium in the stomach and releases magnesium in the intestine in a manner that avoids substantial interaction between the two components." It was also argued, "Tencza discloses a combination of calcium and magnesium which is similar to Richardson and Krishnamurthy, but different from the

present invention. Tencza's combination fails to teach the composition of the present invention which has separate and not combined calcium and magnesium components. The formulations of Tencza do not have a delay release mechanism, which prevents the calcium component and the magnesium component from releasing at the same time and interacting. Richardson, Krishnamurthy and Tencza, either alone or in combination, fail to disclose the sequential release of calcium and magnesium. Moreover, there is no teaching or suggestion in any of these references that would make the present invention obvious to one of ordinary skill in the art."

These arguments have been considered, but were not found to be persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Richardson teaches an oral pharmaceutical composition comprising a dual layer combination tablet which is divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine, whereby the intestine-release portion contains magnesium compounds/magnesium salts and wherein the formulation additionally contains active agents and therapeutic substances, such as calcium and calcium salts. Richardson is

lacking only in the sense that he does not explicitly teach the instant selection of calcium salts. Krishnamurthy and Tencza, were both solely relied upon for the generic teaching that it is well known to use particular calcium salts, as those instantly claimed, in a formulation along with magnesium compounds. Krishnamurthy and Tencza were not relied upon to demonstrate the sequential release of calcium and magnesium, since Richardson has initially met that requirement as stated above. Both Krishnamurthy and Tencza teach various calcium forms as recited in applicant's claims 13, 14 and 18. The prior art (Richardson) teaches a formulation for controlling or sustaining the release of magnesium into a post-gastric environment and release only in the intestine. The secondary references (Krishnamurthy, Tencza) recognize and teach the known calcium components as those instantly recited. The prior art teaches a similar formulation comprising similar ingredients with an equivalent intended purpose as the applicants. Hence, the instant invention is rendered obvious and unpatentable over the prior art of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns
November 05, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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